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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,360	11/03/1999	Hamiduddin Khoja	1544.003	2446

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/433,360	KHOJA ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 10-20* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 6-9 were cancelled, and claims 10-12 were amended, in Paper No. 17, 3/4/2003. Claims 1-5, 10-20 are pending. Claims 1-5, 14-20 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 10-13 are under consideration.

Response to Amendment and Arguments

Applicant's arguments filed in Paper No. 17, 3/4/2003 have been fully considered but they are persuasive in part, for the reasons set forth below.

The rejection of claim 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been rendered moot by cancellation of the claim, and is thus withdrawn.

The rejection of pending claims 10-13 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,932,445 (Lal et al.) has been obviated by Applicant's amendment, and is thus withdrawn.

The rejection of pending claims 10-13 under 35 U.S.C. 102(b) as being anticipated by Matsuoka et al. (1993) has been obviated by Applicant's amendment, and is thus withdrawn.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-13 stand rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility, for reasons of record set forth in Paper No. 15, 8/28/2002. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The rejection of record set forth that it is clear from the instant specification that the nucleic acid encoding the VSHK-1 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 18, line 11). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork

et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, even if, *arguendo*, the nucleic acid encoding the VSHK-1 protein is found to be a G-protein coupled receptor, it is an orphan receptor. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the VSHK-1 protein, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. In the instant case, the fact that the claimed invention encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific ligand for each receptor is known, unless the biological activity of the receptor is disclosed and unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility.

The specification asserts several allegedly patentable utilities for the claimed nucleic acid encoding VSHK-1 polynucleotide. The Specification asserts that the nucleic acid of the instant application can be used in diagnostic assays to detect VSHK-1 polypeptide or mRNA expression in a biological sample (Specification at 42). However, this asserted utility is credible and substantial but not specific. Hybridization probes can be designed from any polynucleotide sequence. Further, the specification does not disclose specific cDNA or DNA targets.

The specification further asserts that the nucleic acid of the instant application can be used in screening assays to identify agents which modulate VSHK-1 receptor signal activity, VSHK-1 ligands, or levels of mRNA encoding VSHK-1 (Specification at 46). However, this asserted utility is credible but not specific or substantial. Such assays can be performed with any polynucleotide. Nothing is disclosed about how the polynucleotide is affected by the compounds, which in turn affect production of mRNA and polypeptide. Additionally, the specification discloses nothing specific or substantial for the mRNA and polypeptide produced in this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

The specification further asserts that the nucleic acid of the instant application can be used to treat certain diseases with compositions which modulates VSHK-1 receptor signal activity, VSHK-1 ligands, or levels of mRNA encoding VSHK-1 (Specification at 55). However, this asserted utility is specific but not substantial or credible. The specification does not disclose diseases associated with altered VSHK-1 activity. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. There is no disclosure, for example, of whether the compounds could be administered orally or parentally, dosages, how to assay for improvement or intolerable levels of side effects, etc. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly

analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide that has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as VSHK-1, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is known to be structurally analogous to proteins that are known in the art as G protein coupled receptors. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances that inhibit its activity is clearly to use it as the object of further research that has been determined by the courts to be a non-patentable utility. Since the instant

specification does not disclose a "real world" use for VSHK-1 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 10-13 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues that the specification set forth three possible biological activities: i) mediation of chemotaxis of immune system cells; ii) involvement in angiogenesis; iii) involvement in glycosaminoglycan production. Applicant then cites a post-filing reference that shows that a polypeptide identical to the polypeptide encoded by the nucleic acid of the instant claims is a functional receptor for the monocyte chemoattractant protein family of chemokines (Scherickart et al.). Applicant then argues that this biological activity was asserted in the specification and confirmed by the Scherickart et al. reference, and that the claimed polynucleotide thus has a specific and substantial utility.

According to MPEP 2107, in order for Applicant to rebut the rejection for lack of utility imposed because the invention lacks an asserted specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility, Applicant must provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing. The examiner should also ensure that there is an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed. That is, the applicant has the

burden to establish a probative relation between the submitted evidence and the originally disclosed properties of the claimed invention.

In the instant case, since the evidence that Applicant cites which demonstrates that the VSHK-1 polypeptide is a receptor for monocyte chemoattractant proteins, is a post-filing date reference, it does not establish that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing. It shows instead that while the Appiocation was filed 11/03/1999, it was not until the publication by Scherickart in 2001 that the claimed polynucleotide had a well-established utility. Furthermore, there is not an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed. One of the asserted biological activities set forth in the specification was that the VSHK-1 polypeptide may play a role in mediation of chemotaxis of immune system cells, they contemplate that the VSHK-1 polypeptide may play a role in chemotaxis in seven different cell types, only one of which is monocytes. Thus, the specification did not disclose a specific role that VSHK-1 may play in a specific biological activity, but rather, broadly contemplated a possible role in a disparate listing of many cells, thus not providing sufficient evidence that a specific and substantial utility based on an association and role in any biological process was known at the time of filing. The specification does not assert that the VSHK-1 polypeptide would bind monocyte chemoattractant proteins; the specification only asserts that the VSHK-1 polypeptide may play a role in chemotaxis of immune cells, one of which are monocytes. It is not clear that this establishes a nexus between the assertion in the specification that the VSHK-1 polypeptide may play a role in chemotaxis of immune cells and the post-filing evidence that the VSHK-1 polypeptide binds monocyte

chemoattractant proteins. Thus, there is not an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Pending claims 10, 12-13 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding an amino acid of SEQ ID NO: 2, or a nucleic acid with the sequence as set forth in SEQ ID NO: 1, does not reasonably provide enablement for a nucleic acid comprising 1500 nucleotides of SEQ ID NO: 1, for reasons of record set forth in Paper No. 15, 8/28/2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection of record set forth that claims 10, 12-13 are overly broad since insufficient guidance is provided as to which of the myriad of variant nucleic acids encode polypeptides which will retain the characteristics of VSHK-1. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of VSHK-1. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a

single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

The rejection of record set forth that given the breadth of claims 10, 12-13 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Applicant argues that the claims are enabled for the encompassed scope given the addition of the limitation wherein the polynucleotide contains at least 1500 contiguous nucleotides of SEQ ID NO: 1. Applicant argues that several working examples are provided, and that undue experimentation would not be required to use the polynucleotides to express a full length VSHK protein. However, the claims as presented do not contain any functional limitation which the polynucleotides encompassed by the claims must possess, nor that any encoded polypeptide must possess. Additionally, the claim language is open, that is, it encompasses polynucleotides that encode new polypeptides with unknown properties. Since the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional

requirements of the encoded polypeptide is lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims. Therefore it would require undue experimentation by one of skill in the art to make and use the invention as claimed without further guidance as to the function which either the polynucleotide or the encoded polypeptide must possess. This rejection could be obviated by limiting the claims to a polynucleotide comprising the coding region of the polynucleotide (i.e. 84-1131), wherein the polynucleotide encodes a full-length polypeptide, since this would set forth the critical structural and functional properties for the claimed nucleic acid.

Pending claims 10, 12-13 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in Paper No. 15, 8/28/2002. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims. The claims are drawn to a nucleic acid which comprises at least 1500 contiguous nucleotides of SEQ ID NO: 1. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded SEQ ID NO: 2. Thus, the scope of the claim includes numerous structural variants, and the genus is

highly variant because a significant number of structural differences between genus members are permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid with a sequence as set forth in SEQ ID NO: 1, and the polypeptide of SEQ ID NO: 2 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant argues that the specification describes a representative number of species and that the specification recites structural features common to all members of the claimed genus. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides. There

is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the claims do not set forth any functional limitation that the polynucleotides, or the encoded polypeptides must posses sufficient to distinguish the polynucleotides of the instant claims from other in the class. Additionally, the claim language is open, that is, it encompasses polynucleotides that encode new polypeptides with unknown properties. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed: there is no guidance in the art as to what the defining characteristics of the polynucleotides or encoded polypeptides might be. Thus, no identifying characteristics or properties of the instant polynucleotides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of SEQ ID NO: 1 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. This rejection could be obviated by limiting the claims to a polynucleotide comprising the coding region of the polynucleotide (i.e. 84-1131), wherein the polynucleotide encodes a full-length polypeptide, since this would set forth the critical structural and functional properties for the claimed nucleic acid.

Conclusion

Claims 10-13 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
May 19, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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